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Effects of Methemoglobin Formers on Spontaneous Locomotor Activity and Methemoglobin Levels in Mice

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13. ABSTRACT (*Maximum 200 words*)
Cyanide (CN) remains a viable threat as a chemical warfare agent. Methemoglobin (MHb) formation is one strategy used to counter CN toxicity. It has been suggested that blood levels of 5-12% MHb will protect a human against a 2X MLD (median lethal dose) of CN. Available MHb formers present certain drawbacks and limitations. To identify improved MHb formers, we characterized the locomotor activity effects and MHb formation capacity of three MHb formers with established efficacy against CN (p-aminopropiophenone [PAPP], p-aminoheptanoylphenone [PAHP] and p-aminooctanoylphenone [PAOP]) as a function of time, dose (9.4-125.0 mg/kg) and route of administration (IM versus IP). Mice received a single injection of a test compound or its solvent, and were either placed in an automated activity monitoring chamber for 1 hr or monitored for MHb levels for 3 hr. Sodium nitrite (100 mg/kg) served as the positive control. Dose-related MHb formation was observed for each compound. A typical time-dependent decline in activity was exhibited in negative control groups and in drug-treated groups that exhibited greater than 20% MHb. A route of administration effect was also observed with PAHP and PAOP. These locomotor activity data, combined with other findings, support the idea that compounds producing low MHb levels can be effective against CN without debilitating side effects.

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INTRODUCTION

Cyanide (CN) has been used as an offensive weapon during wartime, and largely due to its rapid toxicity onset, cost, relative ease of manufacture, and the varied methods of application, CN remains a viable threat as a chemical warfare agent (Compton, 1987; United States Senate Hearings, 1989; McKay and Vogel, 1992). One strategy to counter CN toxicity is to administer compounds that form methemoglobin (MHb), either as a prophylactic or as a treatment after poisoning. Although MHb cannot transport oxygen, properly monitored induced (i.e., acquired) methemoglobinemia can be effective in mitigating and/or reversing CN effects (ATSDR, 1993).

Clinical and experimental evidence document that sodium nitrite ($NaNO_2$) is an efficacious MHb former commonly used to counter CN toxicity (Hug, 1933a,b; Wendel, 1933, Chen et al., 1934). However, Kiese and Weger (1969) measured MHb levels in humans treated intravenously with the recommended dose of $NaNO_2$ (4.0 mg/kg). They reported an average peak MHb level of 7%, a level they considered too low to effectively counter CN toxicity (see also Frankenberg, 1982 and Canfield et al., 1987). Furthermore, this peak value of MHb was not observed until approximately 30 min postinjection (Kiese and Weger, 1969). Finally, cardiac perturbations (Kiese and Weger, 1969) and vasomotor collapse (Weiss et al., 1937) have been observed in humans following $NaNO_2$ administration. A safer and perhaps faster acting MHb former is, therefore, indicated.

As part of an attempt to identify an alternative to $NaNO_2$, three MHb-forming phenones (p-aminopropiophenone, PAPP; p-aminoheptanoylphenone, PAHP; and p-aminooctanoylphenone, PAOP), previously shown to be efficacious against CN (Table 1; also see Scharf et al., 1992), were studied in mice.

The pattern of MHb produced by PAPP, PAHP and PAOP, as well as by $NaNO_2$, was evaluated as a function of time, dose and route of administration. In addition, since the MHb molecule cannot transport oxygen, locomotor activity was examined in separate groups of mice as a gross indicator of functional integrity.

MATERIALS AND METHODS

GENERAL

Male CD-1 Swiss mice (20-37 gm) served as subjects, and were maintained under an AAALAC-accredited animal care and use program. Prior to experimentation, animals were housed in polycarbonate cages in a temperature- ($22^0 \pm 2^0$C) and humidity-controlled (40-70%) housing facility with a 12-hr light/dark lighting cycle with no twilight. Food and water were available *ad libitum* until testing commenced.

METHEMOGLOBIN STUDIES

Each animal received a single intramuscular (IM) or intraperitoneal (IP) injection of PAPP, PAHP or PAOP. Positive controls received an IM or IP injection of sodium nitrite, whereas negative controls received an IM or IP injection of vehicle only (see Table 2).

Blood samples (40 Fl) were obtained from the tail of each subject at -2, +2, +15, +30, +60, +120, and +180 min relative to injection. The first sample provided baseline information. Subsequent time points were selected to encompass anticipated time of action of the test compounds and to provide an adequate number of intermediate measurements for ascertaining temporal patterns of MHb formation. Each sample

TABLE 1. Efficacy of the phenones against a 2 X MLD CN challenge. * p< 0.05 vs. 0.0 mg/kg controls.

TREATMENT CONDITION	DOSE mg/kg	SURVIVAL[1]	
		15 min[2]	60 min
PAPP	Positive Control[3]	-	10/10*
	0.0[4]	1/10	0/10
	9.4	9/10*	0/10
	11.7	10/10*	0/10
	37.5	10/10*	9/10*
	150.0	8/10*	10/10*
PAHP	Positive Control	-	10/10*
	0.0	1/10	0/10
	15.6	10/10*	4/10*
	62.5	9/10*	10/10*
	250.0	2/8	2/8
PAOP	Positive Control	-	10/10*
	0.0	1/10	0/10
	7.5	0/10	0/10
	13.0	3/10	0/10
	30.0	10/10*	10/10*
	52.5	10/10*	10/10*
	120.0	10/10*	7/10*
	210.0	5/10*	5/10*

[1] Survival was determined 24 hr after CN exposure.
[2] Compounds were administered IP, 15 min or 60 min prior to CN exposure.
[3] Animals serving as positive controls received sodium nitrite (100 mg/kg) and sodium thiosulfate (1000 mg/kg), co-administered 60 min prior to CN exposure.
[4] 0.0 mg/kg control animals (i.e., negative controls) received the appropriate solvent only.

was analyzed for MHb using an OSM3 Hemoximeter (Radiometer America, Inc., Westlake, OH). For each compound separate analyses were performed for IM and IP groups. In addition, for each compound and its respective vehicle, a repeated measures analysis of variance (ANOVA) was performed (dose X time), with time as the repeated measure. Simple main effects analyses and/or Newman-Keuls tests were performed as appropriate. All tests were considered statistically significant at the $P < 0.05$ level.

LOCOMOTOR ACTIVITY STUDIES

Each phenone-treated animal received a single IM or IP injection of PAPP, PAHP or PAOP, as available. Positive controls received an IM or IP injection of sodium nitrite,

whereas negative controls received an IM or IP injection of vehicle only (see Table 2).

Immediately following injection, and continuing for 60 min, activity was monitored (in 12 5-min blocks) in individual test chambers interfaced with a Digiscan Analyzer (Omnitech Electronics, Inc, Columbus, OH). For each compound separate analyses were performed for IM and IP data. In addition, for each compound and its respective vehicle, a repeated measures ANOVA was performed (dose X time), with time as the repeated measure. Newman-Keuls were conducted as appropriate. All tests were considered statistically significant at $P < 0.05$.

TABLE 2. MHb-forming compounds administered IM or IP in mice. Injection volume was 0.5 ml/kg for IM and 1.0 ml/kg for IP. For MHb studies, N = 5-19/group; for locomotor activity studies, N = 5-8/group. Note that not all dose/route combinations were assessed in each experiment.

COMPOUND	VEHICLE	DOSE (mg/kg)
PAPP	5% EtOH/PEG 200	9.4, 11.7, 18.8, 37.5
PAHP	5% EtOH/PEG 200	15.6, 31.2, 62.5, 125.0
PAOP	PEG 200	30.0, 45.0, 52.5, 60.0, 90.0
$NaNO_2$	SALINE	100.0

RESULTS

Animals treated with PAPP (IM, IP), PAHP (IP) or PAOP (IP) exhibited large (>15%) and time- and/or dose-related increases in MHb. This observation was supported by a significant dose X time interaction. However, animals treated IM with PAHP or PAOP exhibited a small (<8%) but statistically significant dose-related increase in MHb or no significant changes in MHb, respectively (see Figure 1). Observed MHb changes were typically longer lasting following injections of PAHP (IM, IP) or PAOP (IP), as compared with injections of PAPP (IM, IP) (see Figure 1).

For the locomotor activity studies, all groups showed a significant decrease in locomotor activity as a function of time. This was supported statistically by a significant main effect of time. However, the phenones did have measurable effects on locomotor activity. Independent of test compound, when corresponding MHb levels exceeded 20%, a statistically significant hypoactivity was generally observed (see Figures 2-6). This was supported by the significant dose X time interaction. The hypoactivity was evident beginning approximately 10 min postinjection. Thus, significant hypoactivity was observed for PAPP (IM and IP) at 18.8 mg/kg and 37.5 mg/kg, and for PAHP (IP only), at 15.6 mg/kg and 31.2 mg/kg. For PAOP (IP only), at 30 mg/kg, there was a trend for hypoactivity, but this was not statistically significant. For the $NaNO_2$ positive control animals, signficant hypoactivity was also observed (see Figure 6). Groups in which corresponding MHb levels were below 20% generally exhibited normal activity, although there was a nonsignificant trend of hyperactivity in PAHP and PAOP animals treated IM (see Figures 2-5).

DISCUSSION

The MHb forming phenones PAPP, PAHP and PAOP each provide dose-related protection in mice against a 2 X MLD CN challenge (Table 1; see also Scharf et al., 1992). In the present study, hypoactivity was observed, but only when MHb exceeded 20%. These data support the contention that efficacious doses of these compounds, which lead to less than 20% MHb, are not behaviorally disruptive. Interestingly, it has been reported that in humans, oxygenation of working muscle is impaired when MHb levels exceed 20% (Tepperman et al., 1946), although Paulet et al. (1963) reported no ill-effects of doses of PAPP generating up to 48% MHb.

Furthermore, the pattern of protection produced by these phenones, combined with the time-course MHb data, is consistent with the notion that MHb formation is necessary for these compounds to be effective against CN. For $NaNO_2$, the observed hypoactivity is generally consistent with previous reports in rabbits (Haldane et al., 1897) and rodents following either injections (Freeman et al., 1986; Hlinak and Krejci, 1990) or administration via drinking water (Gruener and Shuval, 1972).

Interestingly, when MHb levels remained below 20%, either no changes in activity or trends of mild hyperactivity were observed. The hyperactivity, however, was limited to those groups of animals in which little or no MHb was detected (i.e., PAHP or PAOP, administered IM). Indeed, phenone carbon chain-length and route of administration were critical variables associated with specific effects on MHb formation and related changes in locomotor activity. The phenones PAPP and PAHP each produced significant, dose-related MHb and locomotor hypoactivity when administered IP. In addition, a trend for locomotor hypoactivity was observed for PAOP administered IP, but this was not statistically significant. However, the longer the carbon chain, the less likely it was that IM-treated animals would exhibit significant MHb levels and concurrent locomotor hypoactivity. This observation deserves further attention, since there is apparent drug sequestration or another mechanism operating by which these compounds are not readily available when administered via the IM route. Finally, hematologic effects other than changes in MHb must also be taken into consideration, such as oxyhemoglobin, sulfhemoglobin, reduced hemoglobin and oxygen content (Rockwood et al., 1996).

PAPP

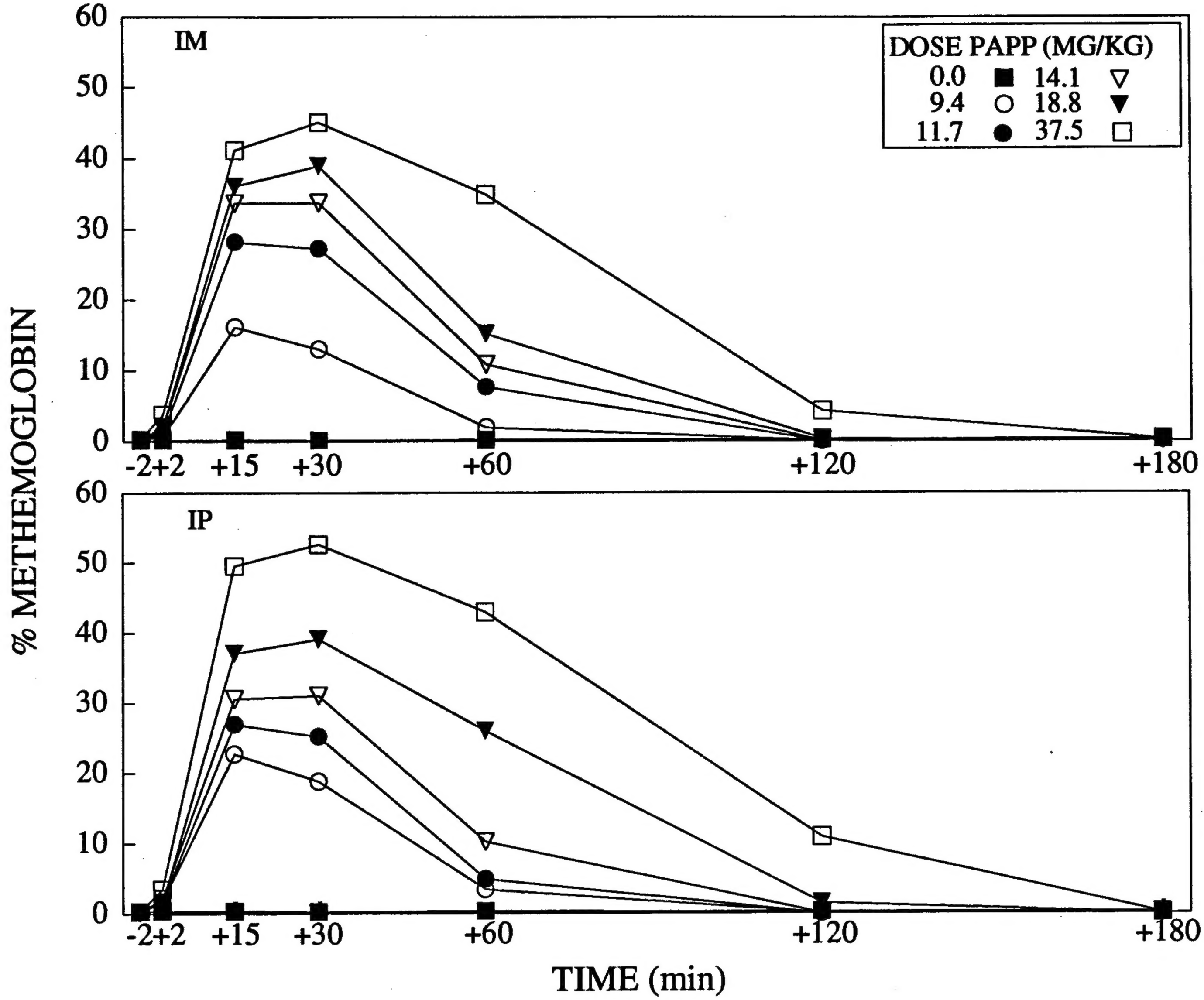

Figure 1a. MHb levels in mice treated with PAPP, as of function of dose, time and route of administration.

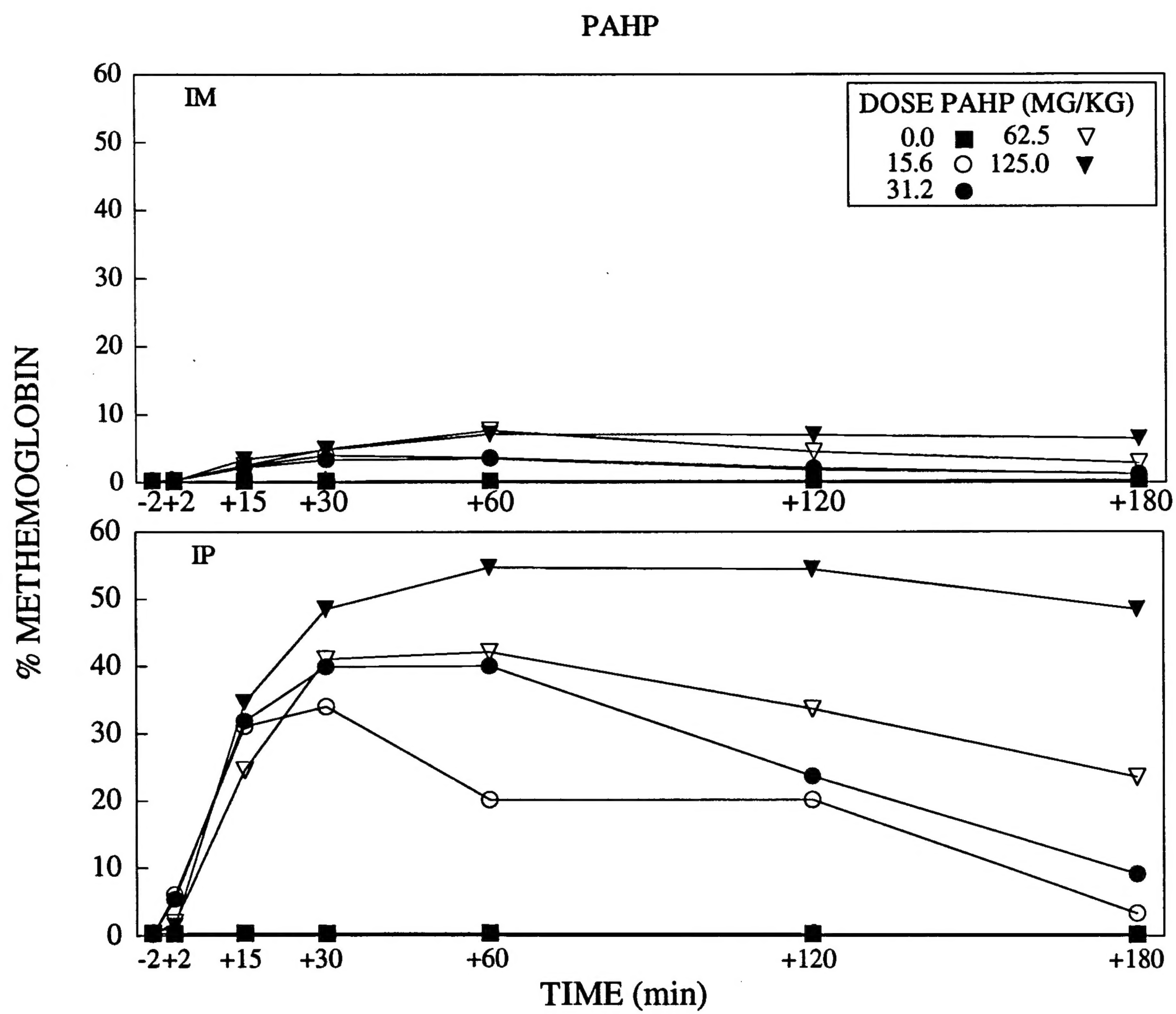

Figure 1b. MHb levels in mice treated with PAHP, as of function of dose, time and route of administration.

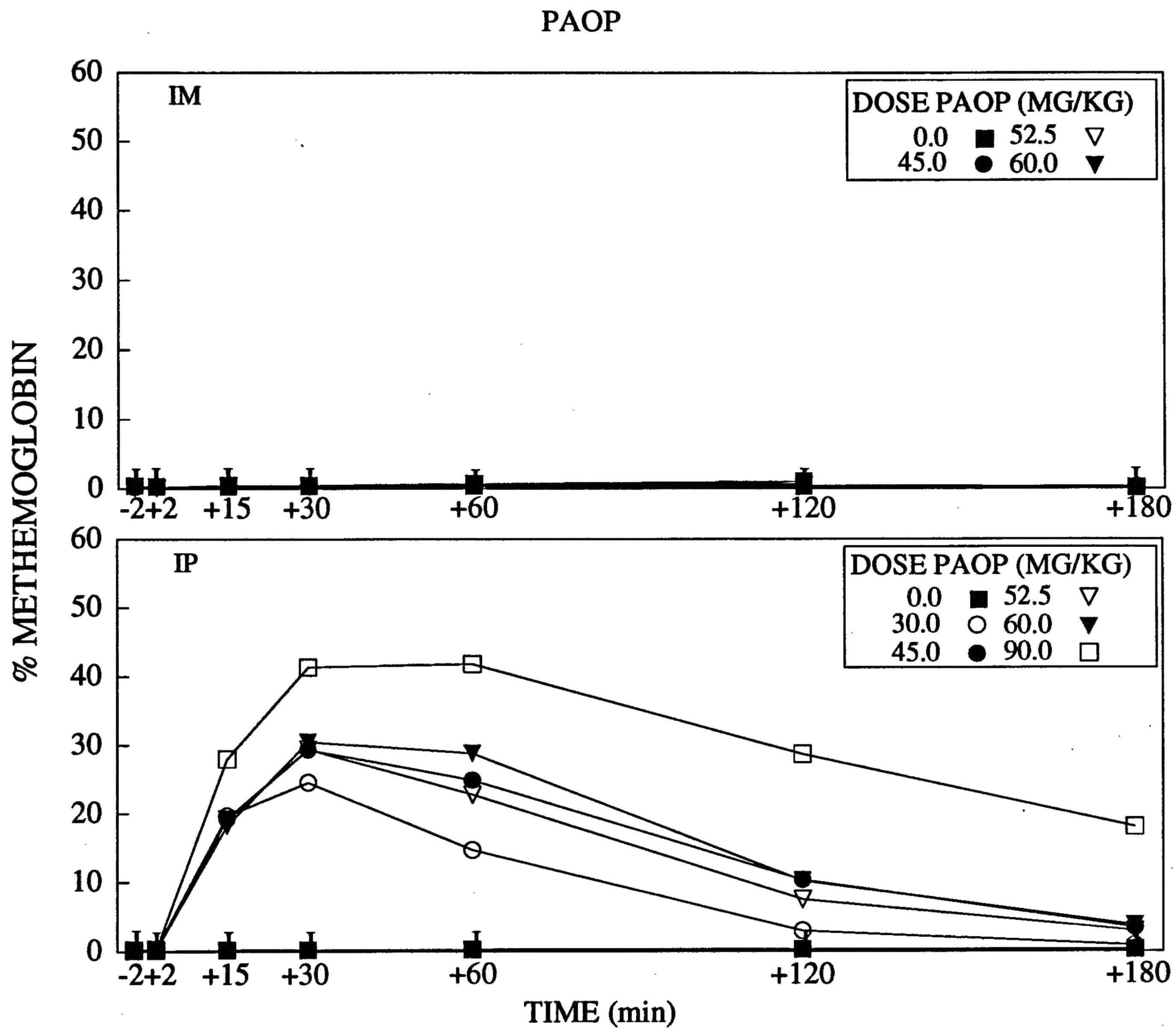

Figure 1c. MHb levels in mice treated with PAOP, as a function of dose, time a route of administration.

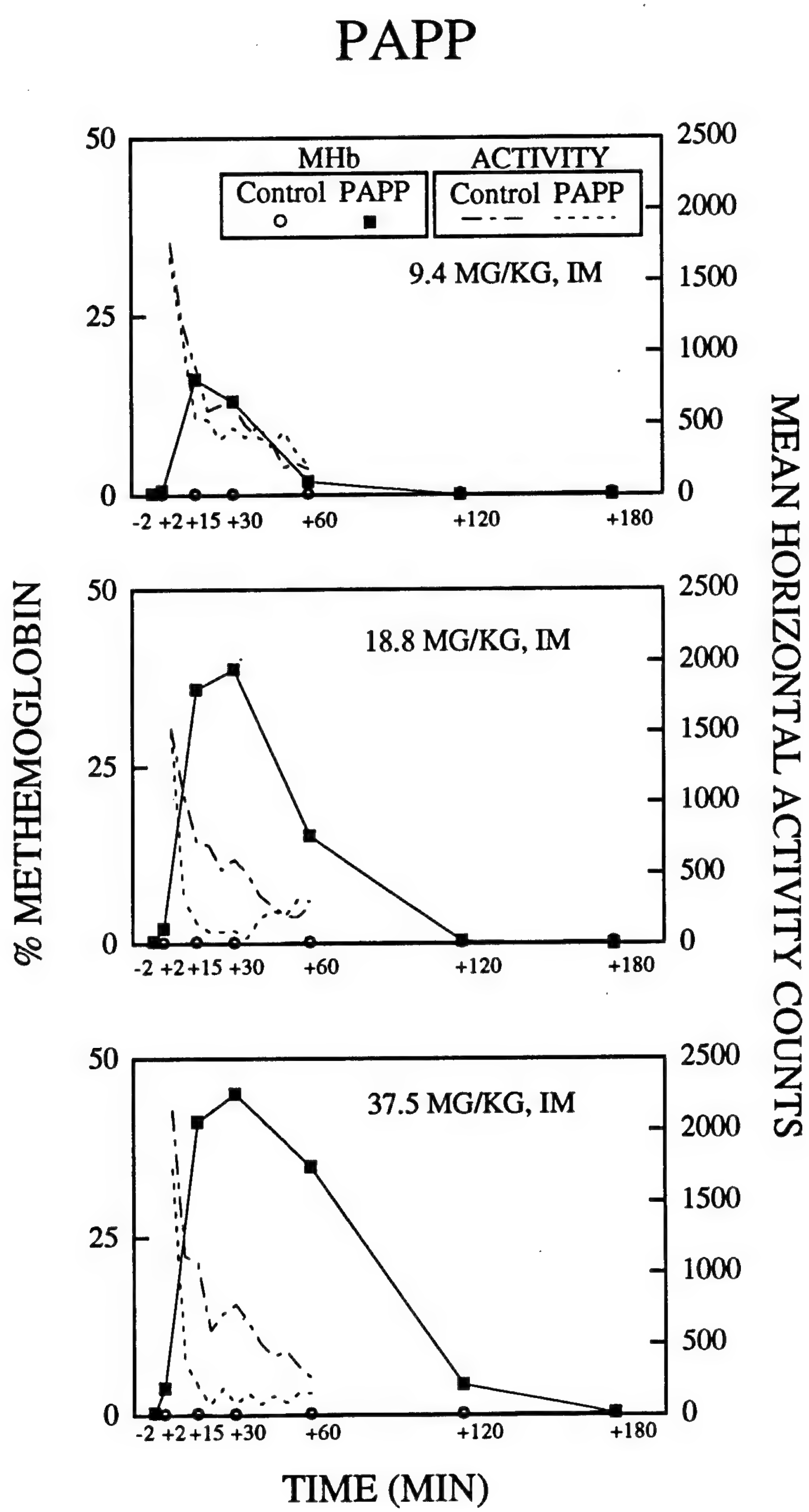

Figure 2. Locomotor activity levels in mice treated IM with PAPP as a function of dose and time. These data are representative of PAPP-induced hypoactivity. IP data are similar. MHb levels of similarly treated animals are also shown.

PAHP 15.6 mg/kg

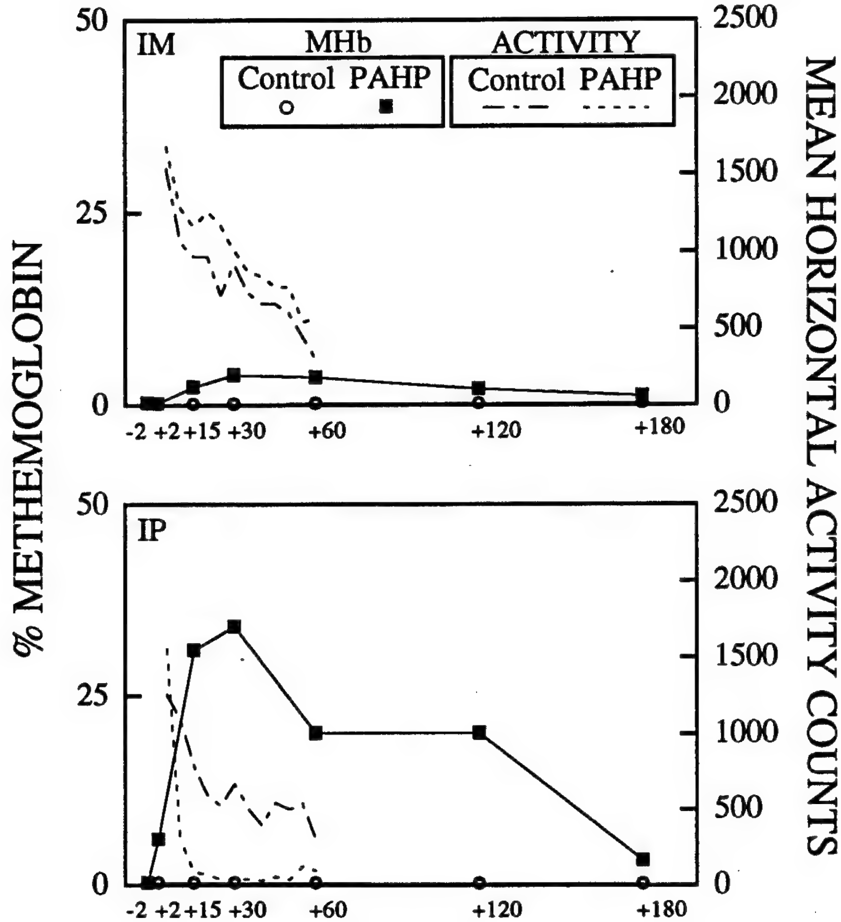

Figure 3. Locomotor activity levels in mice treated with 15.6 mg/kg PAHP, as a function of time and route of administration. The IP data are representative of PAHP-induced hypoactivity. MHb levels of similarly treated mice are also shown.

PAHP 31.2 mg/kg

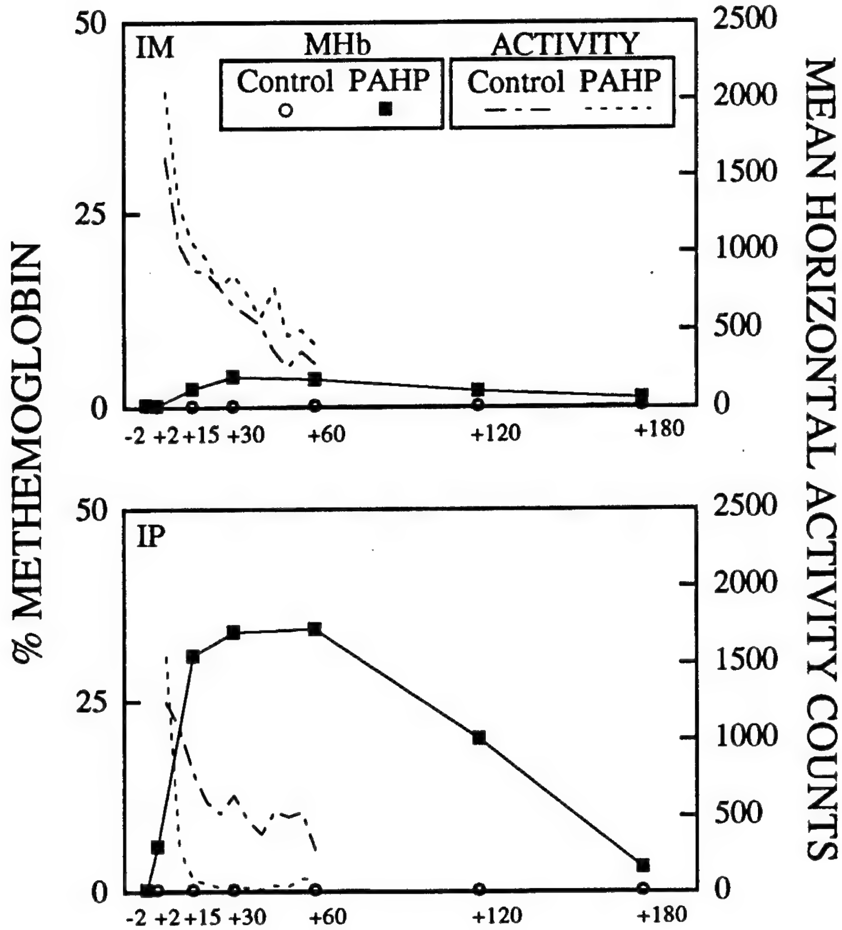

Figure 4. Locomotor activity levels in mice treated with 31.2 mg/kg PAHP, as a function of time and route of administration. The IP data are representative of PAHP-induced hypoactivity. MHb levels of similarly treated mice are also shown.

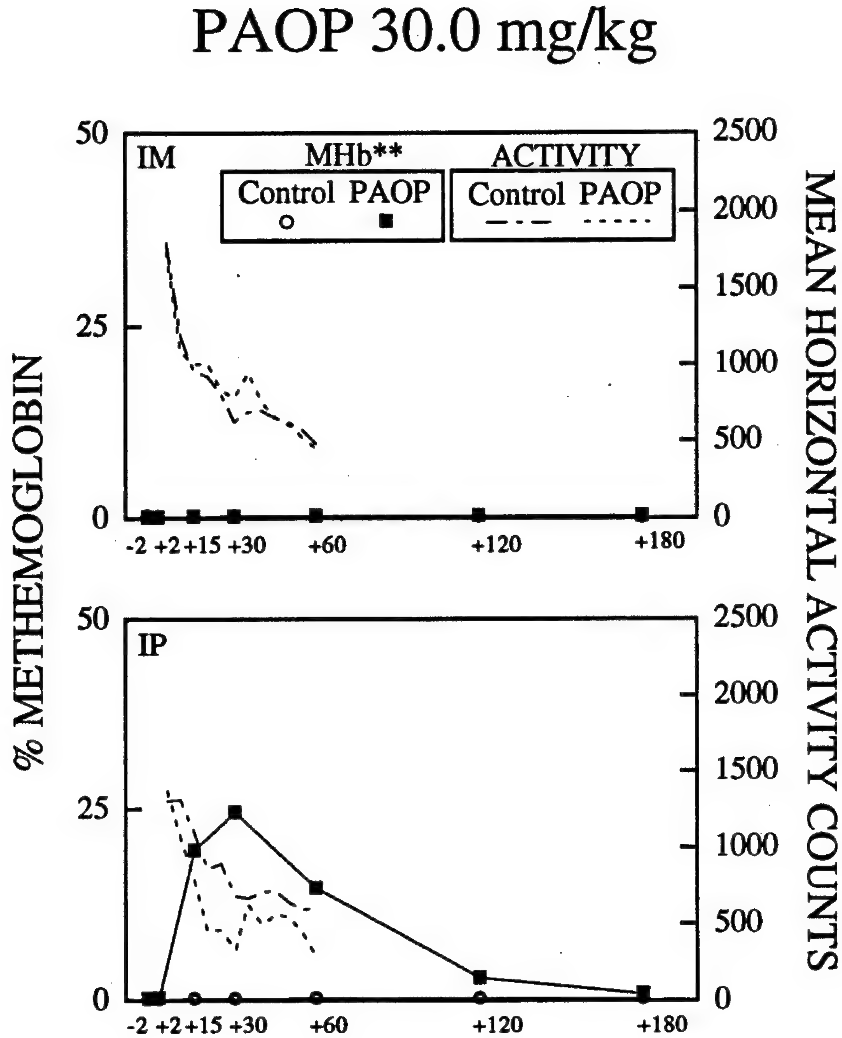

Figure 5. Locomotor activity levels in mice treated with 30.0 mg/kg PAOP, as a function of time and route of administration. The IP data are representative of PAOP-induced hypoactivity. MHb levels of similarly treated mice are also shown. **For IM, no animals were tested at 30.0 mg/kg; therefore the data included on the IM panel for MHb represent animals treated with PAOP at 45.0 mg/kg.

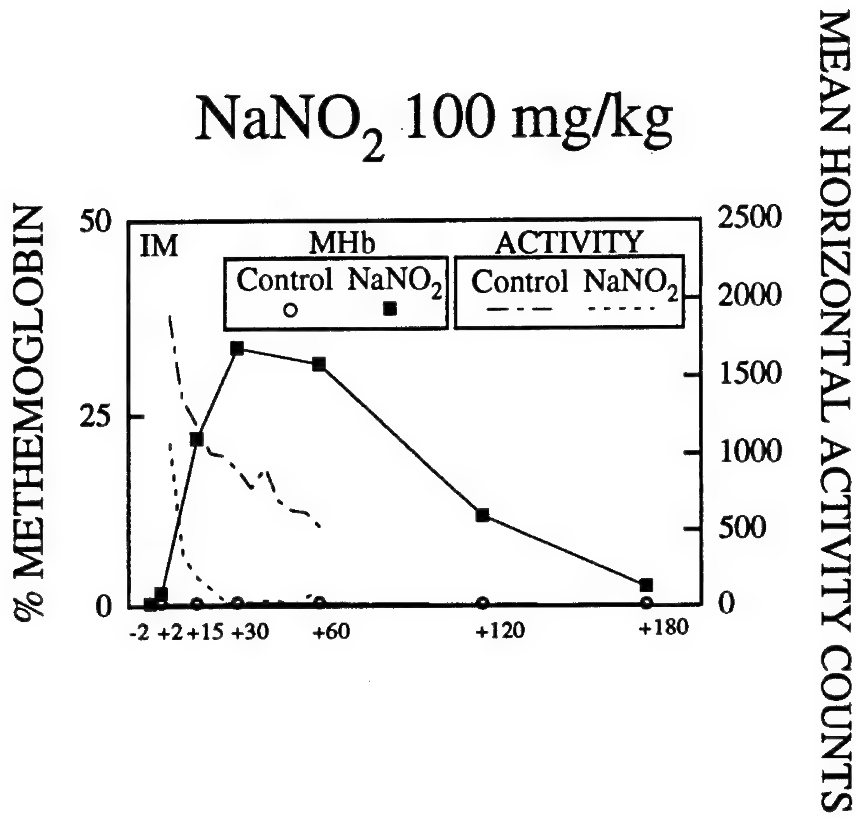

Figure 6. Locomotor activity levels in mice treated IM with 100.0 mg/kg $NaNO_2$, as a function of time. IP activity data are similar. MHb levels of similarly treated mice are also shown.

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